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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/776,874	02/06/2001	Iris Pecker	01/21603	8407

7590 10/03/2005

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EXAMINER	
HUTSON, RICHARD G	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/776,874	PECKER ET AL.	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71,72,92-101,107-111 and 114-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71,72,92-101,107-111 and 114-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

820

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/21/2005 has been entered.

Applicants amendment of claims 72, 97 and 107, cancellation of claims 64-67, 76-78, 80-91, 102-106, 112 and 113 and the addition of new claims 114-118, in the paper of 7/21/2004, is acknowledged.

Claims 71, 72, 92-101, 107-111 and 114-118 are at issue and are present for examination.

Applicants' arguments filed on 7/21/2005 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

Claims 71, 72, 92-101, 107-111 and 114-118 are objected to because of the following informalities:

Claims 71, 72, 92-101, 107-111 and 114-118 each recite "wherein said polypeptide includes..." This is interpreted as "wherein said polypeptide comprises..."

and it is suggested that applicants amend the claims as such to be more in alignment with the standard that is used in the art.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 71, 72, 92-94, 96-100, 107-110 and 114-117 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a protein or preparation comprising said protein having the amino acid sequence of SEQ ID NO: 10, said protein having heparanase activity or being so cleavable so as to acquire said heparanase activity, does not reasonably provide enablement for any protein or preparation comprising said protein having heparanase activity or being so cleavable so as to acquire said heparanase activity, wherein said protein is merely 70% homologous to SEQ ID NO: 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection was made in the previous office action as it applied to previous claims 64-67 and 70-79. In response to this rejection applicants have amended claims

72, 97 and 107, canceled claims 64-67, 76-78, 80-91, 102-106, 112 and 113 and added new claims 114-118 and traverse the rejection as it applies to the new claims.

Applicants initial comments regarding the scope of meaningful protection and the relationship of such to potential infringers are acknowledged. Applicants are reminded that such is not the basis of the rejection of record and is of limited use in applicants traversal of the rejection.

Applicants continue to traverse the rejection on the basis that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled and that applicants disclosure of the human, mouse and rat polypeptide sequences, as well as the associated alignment information results in ample guidance for the "expenditure of no more effort than is normally required in the art. Applicants reference the alignment data of the three variant species disclosed and submit that this provides ample guidance to enable the skilled artisan to make active heparanase variants.

Applicants complete argument is acknowledged, however found nonpersuasive for the reasons previously made of record.

Applicants continued submission, that applicant has submitted alignment data showing the homology between human, rat, mouse and chicken heparanase sequences as well as important shared features is acknowledged. While this information is helpful in enabling the claimed genus, by itself it appears to be insufficient to do such.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated

with the scope of the claims broadly including any number of amino acid modifications of any heparanase having a mere 70% homology to SEQ ID NO: 10.

As previously stated, while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants useful as heparanases requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the activity. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. For the rejected claims would clearly constitute undue experimentation. Guo et al. (H. Guo et al., "Protein Tolerance to Random Amino Acid Change", PNAS 101(25): 9205-9210, June 2004) teach that the percentage of random single substitution mutations which inactivate a protein for the protein 3-methyladenine DNA glycosylase is 34% and that this number appears to be consistent with other studies in other proteins as well. Guo et al. further show in Table 1 that the percentage of active mutants for multiple mutants appears to be exponentially related to this by the simple formula $(.66)^x$ X 100% where x is the number of mutations introduced. Applying this estimate to the instant protein, 80% identity allows up to 109 mutations within the 543 amino acids of SEQ ID NO:10 and thus only $(.66)^{109}$ X 100% or 2.1×10^{-18}% of random mutants having 80% identity would be active. Similarly at 85% identity only 2.43×10^{-13}% would be active, at 90% identity, 3.4×10^{-9}% would be active and at 95% identity 1.3×10^{-3}%. Current techniques (i.e., high throughput mutagenesis and screening techniques) in the art would not allow for finding the few active mutants within the several hundred

thousand to greater then several trillions of inactive mutants, as is the case for the claims limited to 70% identity. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any heparanase having a mere 70% homology to SEQ ID NO: 10. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 71, 72, 92-101 and 107-111 are rejected under 35 U.S.C. 102(b) as being anticipated by Fuks et al. (U.S. Patent No. 5,362,641).

The rejection was originally stated in the previous office actions, 10/21/2003, 7/1/2003 and 12/17/2003. In response to this rejection applicants have amended claim 72, 97 and 107, canceled claims 64-67, 76-78, 80-91, 102-106, 112 and 113 and the added new claims 114-118 and traverse the rejection as it applies to the new claims. Newly added claims 114-118 are included in the rejection for the same reasons previously stated for claims 64-67 and 70-79.

In applicants traversal, applicants note that applicants have four sets of claims pending and make four distinctions of Fuks based on these claim sets. Applicants continue to traverse along many of the lines of argument presented in the previous office action(s).

First, applicants submit that claims 97-101, as currently amended, are directed to a preparation that "can elicit anti-heparanase antibodies" and that as stated in previous responses and declarations, Fuks could not elicit anti-heparanase antibodies. Applicants submit that applicants claims are not directed to a preparation with the "potential" to elicit anti-heparanase antibodies but rather to a preparation that "can" elicit antibodies.

This argument is a continuation of that previously presented by applicants based on the argument that the antibodies raised in Fuks in an attempt to prepare anti-heparanase antibodies were actually anti-PAI-1 antibodies. As has been previously stated, this is acknowledged, however, it continues to be the position of the office that,

though not 100% pure, the preparation taught by Fuks et al. is that of "an isolated heparanase", from the same source as applicants claimed heparanase protein, and thus Fuks et al. anticipates applicants claimed "isolated heparanase protein" for all of the reasons of record.

Applicants attempt to distinguish between those preparations that "have the potential" to elicit antibodies and those preparations that "can" elicit antibodies is not found persuasive.

Second, applicants continue to submit that in contrast to the subject matter of claims 107-110, the heparanase taught by Fuks is not purified "close to homogeneity". Applicants continue to submit that no one skilled in the art would consider the preparation of Fuks "close to" homogeneity or purity, because the heparanase of Fuks was inextricably mixed with a significant amount of at least six other proteins (See previous declarations).

This line of argument is not found persuasive for the reasons previously stated.

In spite of applicants interpreted definition of what it is to be "close to" homogeneity, it remains unclear as to what one of ordinary skill in the art would consider "close to homogeneity" as opposed to what one of ordinary skill in the art would consider "homogeneous". Applicants submission that the heparanase preparation of Fuks was "contaminated" with at least six other proteins, does not distinguish from the claimed purity of heparanase preparation and given the environment that the heparanase originally started (i.e. in a cell or a cell extract), it continues to be understood that the preparation of Fuks is "close to" homogeneity.

Thus those claims reciting such a limitation continue to be anticipated by Fuks et al. because while applicants present evidence that the protein composition taught by Fuks et al. was not "homogeneous", it remains to be shown if that composition taught by Fuks et al. was not "close to homogeneity". Applicant is reminded that the office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicants, thirdly and fourthly submit that claims 114-118 are directed to a "purified" or 'isolated" heparanase and "pure" or "isolate" is defined as containing no contaminating material. Applicants continue to submit that the heparanase of Fuks was far from "pure" and far from being "isolated", as it was mixed with significant amounts of contaminating material. While applicants continued argument is acknowledged, it is not found persuasive for the reasons previously stated, and it remains that Fuks et al. continues to anticipate those claims directed to a "purified" heparanase as well as those claims to an "isolated" heparanase Fuks et al. teach a "purified heparanase".

Thus applicants argument has been considered in full and found to be non-persuasive.

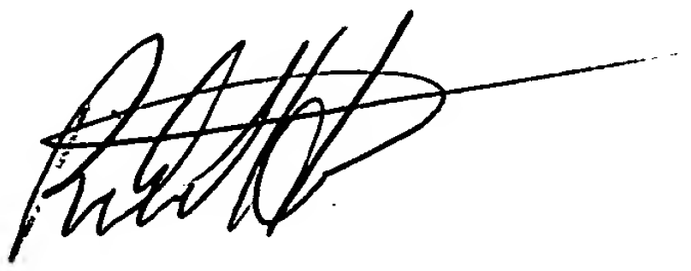
Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
9/21/2005